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Comparison of American and European Guideline Recommendations for Diagnostic Workup and Secondary Prevention of Ischemic Stroke and Transient Ischemic Attack

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ABSTRACT: Guidelines help to facilitate treatment decisions based on available evidence, and also to provide recommendations in areas of uncertainty. In this paper, we compare the recommendations for stroke workup and secondary prevention of ischemic stroke and transient ischemic attack of the American Heart Association (AHA)/American Stroke Association (ASA) with the European Stroke Organization (ESO) guidelines. The primary aim of this paper is to offer clinicians guidance by identifying areas where there is consensus and where consensus is lacking, in the absence or presence of high-level evidence. We compared AHA/ASA with the ESO guideline recommendations for 7 different topics related to diagnostic stroke workup and secondary prevention. We categorized the recommendations based on class and level of evidence to determine whether there were relevant differences in the ratings of evidence that the guidelines used for its recommendations. Finally, we summarized major topics of agreement and disagreement, while also prominent knowledge gaps were identified. In total, we found 63 ESO and 82 AHA/ASA recommendations, of which 38 were on the same subject. Most recommendations are largely similar, but not all are based on high-level evidence. For many recommendations, AHA/ASA and ESO assigned different levels of evidence. For the 10 recommendations with *Level A* evidence (high quality) in AHA/ASA, ESO only labeled 4 of these as *high quality*. There are many remaining issues with either no or insufficient evidence, and some topics that are not covered by both guidelines. Most ESO and AHA/ASA Guideline recommendations for stroke workup and secondary prevention were similar. However not all were based on high-level evidence and the appointed level of evidence often differed. Clinicians should not blindly follow all guideline recommendations; the accompanying level of evidence informs which recommendations are based on robust evidence. Topics with lower levels of evidence, or those with recommendations that disagree or are missing, may be an incentive for further clinical research.

Key Words: guidelines ■ ischemic attack, transient ■ ischemic stroke ■ secondary prevention

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Optimal diagnostic stroke workup and secondary prevention are essential to prevent new cardiovascular events after an ischemic stroke or transient ischemic attack (TIA). Many modifiable risk factors are known to be associated with (recurrent) vascular events.[1] New vascular events could be prevented in ≥80%, with optimal secondary prevention in stroke patients.[2] Guidelines help to facilitate treatment decisions based on available evidence, and also provide recommendations in areas of uncertainty. Examples of areas of uncertainty include optimal screening interval and detection method for paroxysmal atrial fibrillation (AF), selection for structural heart disease screening, optimal antithrombotic medication for carotid dissection, treatment of intracranial arterial stenosis, and treatment in moderate and/or asymptomatic carotid disease.

When US and European cardiology guidelines were compared, multiple recommendations diverged, despite

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.124.069651.

For Sources of Funding and Disclosures, see pages 814–815.

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Circulation is available at www.ahajournals.org/journal/circ

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
AHA	American Heart Association
ASA	American Stroke Association
CAS	carotid artery stenting
DAPT	dual antiplatelet therapy
DOAC	direct oral anticoagulant
ESO	European Stroke Organization
PFO	patent foramen ovale
PICO	population, intervention, comparison, outcomes
TIA	transient ischemic attack

being based on the same available evidence.[3,4] In this article, we compare the recommendations for workup and secondary prevention of ischemic stroke and transient ischemic attack of the American Heart Association (AHA)/American Stroke Association (ASA) with the European Stroke Organization (ESO) guidelines. We also discuss methodological differences between guidelines. The primary aim of this article is to offer clinicians guidance by identifying areas where there is consensus and where consensus is lacking, in the absence or presence of high-level evidence.

TOPICS AND SEARCH

First, we screened all ESO and AHA/ASA stroke guidelines for recommendations on stroke workup and secondary prevention across 7 main topics (Table 1). ESO has recently published their first dedicated guidelines on many of these specific topics in the *European Stroke Journal* and ESO website. AHA/ASA stroke guidelines are generally published in *Stroke*, and can be found in their online guideline databases. We only considered formal guidelines from ESO and AHA/ASA and excluded Scientific Statements or Consensus Statements.

In total, we found 9 different ESO guidelines with recommendations on stroke workup and/or secondary prevention,[5–13] one of which was a statement from multiple European associations about sleep disorders. For some topics, recommendations from different ESO guidelines were combined (Table 1).

The 2021 updated AHA/ASA Guideline on Stroke Prevention was originally published in 2014, addressed all topics.[14,15] Three independent reviewers (M.M., T.C., J.S.) initially screened the ESO and AHA/ASA guidelines for recommendations regarding the topics of interest, categorized the recommendations by strength and level of evidence (Table 2), listed the main subjects of agreement and disagreement (Tables 3 and 4), and listed the remaining knowledge gaps (Table 5). Moreover, all guideline recommendations for the 7 different topics were listed and compared by statement, strength, and quality (Tables S1–S7). In cases of disagreement, D.D. and J.B. were consulted for resolution.

GUIDELINE METHODOLOGY

All ESO Guidelines use the Grading of Recommendations, Assessment, Development and Evaluation methodology and have a specific operating procedure for guidelines.[16] The clinical questions are specified (population, intervention, comparison, outcomes [PICO]), and systematic reviews with or without meta-analyses are executed to answer the questions. Each guideline module is assigned a module leader whom is expected to be an experienced stroke-expert for that topic. The quality of evidence is rated from *high* through *moderate* and *low* to *very low*. For the strength of the recommendations the

Table 1. Compared Topics and Used Guidelines With Year of Publication

Topic	ESO Guideline(s)	Year Published
Stroke and TIA workup	Screening for subclinical atrial fibrillation after stroke or transient ischemic attack of undetermined origin Management of transient ischemic attack	2022 2021
Antiplatelet treatment	Management of transient ischemic attack Short-term dual antiplatelet therapy early after minor stroke and high-risk TIA Pharmacologic interventions for long-term secondary prevention after ischemic stroke or transient ischemic attack	2021 2021 2022
Management of cardiac sources	Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and nonvalvular atrial fibrillation	2019
Extracranial carotid interventions	Endarterectomy and stenting for carotid artery stenosis	2022
Dissection	Management of extracranial and intracranial artery dissection	2021
Intracranial artery disease	Treatment of patients with intracranial atherosclerotic disease	2022
Other secondary prevention recommendations	Pharmacologic interventions for long-term secondary prevention after ischemic stroke or transient ischemic attack EAN/ERS/ESO/ESRS statement on the impact of sleep disorders on risk and outcome of stroke	2022 2020

EAN indicates European Academy of Neurology; ERS, European Respiratory Society; ESO, European Stroke Organization; ESRS, European Sleep Research Society; and TIA, transient ischemic attack.

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Table 2. Categorization of Recommendations by Strength and Level of Evidence

ESO		AHA/ASA	
Strength	Level of evidence	Strength	Level of evidence
Strong for/high	6 (10%)	1/A	12 (15%)
Strong for/moderate	6 (10%)	1/B-R	8 (10%)
Strong for/low	2 (3%)	1/B-NR	9 (11%)
Strong for/very low	0	1/C-LD	1 (1%)
–		1/C-EO	4 (5%)
–		2a/A	1 (1%)
–		2a/B-R	10 (12%)
–		2a/B-NR	5 (6%)
–		2a/C-LD	4 (5%)
–		2a/C-EO	1 (1%)
Weak for/high	0	2b/A	1 (1%)
Weak for/moderate	3 (5%)	2b/B-R	5 (6%).
Weak for/low	6 (10%)	2b/B-NR	7 (9%)
Weak for/very low	4 (6%)	2b/C-LD	7 (9%)
–		2b/C-EO	0
Weak against/high	0	3 (no benefit)/A	1 (1%)
Weak against/moderate	0	3 (no benefit)/B-R	2 (2%)
Weak against/low	1 (2%)	3 (no benefit)/B-NR	0
Weak against/very low	2 (3%)	3 (no benefit)/C-LD	0
–		3 (no benefit)/C-EO	0
Strong against/high	0	3 (harm)/A	2 (2%)
Strong against/moderate	1 (2%)	3 (harm)/B-R	2 (2%)
Strong against/low	2 (3%)	3 (harm)/B-NR	1 (1%)
Strong against/very low	2 (3%)	3 (harm)/C-LD	0
–		3 (harm)/C-EO	0
Expert opinion	22 (35%)		See *EO* labels
No recommendation because insufficient evidence	6 (10%)		0
Recommendation without classification	2 (3%)		0
Total recommendations	63		82

For the strength of the recommendations the ESO classifications used *strong* and *weak*, for or against an intervention. AHA/ASA gave a classification of *1* (strong) through *2a* (moderate) and *2b* (weak) to *3* (no benefit or harm). The quality of evidence in ESO guidelines was rated from *high* through *moderate* and *low* to *very low*. AHA/ASA graded levels of evidence from *A* (high quality), through *B-R* and *B-NR* (randomized or nonrandomized) to *C-LD* and *C-EO* (limited data or expert opinion). – indicates that no recommendation was made because of insufficient data.

classifications *strong* and *weak* are used, for or against an intervention. Expert consensus is used for recommendations where evidence was insufficient to support a recommendation based on the type of available evidence and considerations on inconsistency, indirectness, imprecision, and risk of bias (according to the Cochrane assessment tools for randomized and nonrandomized trials). Expert consensus statements are based on majority vote, using the Delphi method. Only statements that had a majority vote are published, and the numbers of committee members agreeing with the recommendation are listed.[17,18] Due to insufficient evidence, some issues do not have related recommendations or expert opinions.

The AHA/ASA recommendations are evidence based and supported by an extensive evidence review. Authors are assigned based on areas of expertise and their lack of any relationships with industry related to the section material. The quality of evidence is graded from *A* (ie, high quality) to *B-R* and *B-NR* (ie, randomized or nonrandomized, respectively) to *C-LD* and *C-EO* (limited data or expert opinion). The strength of a recommendation was designated *Class 1* (strong), *Class 2a* (moderate) and *2b* (weak), or *Class 3* (no benefit or harm). All recommendations were fully reviewed and discussed before a final vote to reach consensus.[15]

OVERVIEW OF RECOMMENDATION STRENGTHS AND LEVEL OF EVIDENCE

We summarized all recommendations from both guidelines by its corresponding strength and level of evidence in Table 2. In total, we compared 63 ESO and 82 AHA/ASA recommendations related to the topics of interest: 38 subjects had recommendations in both guidelines, 25 only had ESO recommendations and 44 only AHA/ASA. Of the recommendations that both guidelines addressed, 10 were classified as *A* (high quality evidence) by AHA/ASA. ESO indicated 4 of these 10 recommendations as having high-level evidence, while 1 had very low-level evidence, and 3 were consensus statements. For the 15 that AHA/ASA labeled as *B-R* (ie, moderate quality based on randomized studies), ESO indicated 1 to have high-, 7 moderate-, and 5 low-quality levels of evidence, and 3 were consensus statements (2 were not comparable because ESO had no level-of-evidence classification). Of the 7 recommendations AHA/ASA labeled as *B-NR* (moderate quality based on nonrandomized studies), ESO had 2 low- and 2 very low-quality evidence, as well as 2 consensus statements, one which had insufficient evidence. Of the remaining 4 *C-LD* (limited data) recommendations from AHA/ASA, ESO had 1 with high- and 1 with low-quality evidence, and 2 consensus statements.

ESO guidelines featured 22 expert opinions in their 63 recommendations (35%). In 6 instances, ESO concluded that no recommendations could be made due to insufficient evidence (10%); while 5 of 82 AHA/ASA recommendations (6%) were expert opinions, of which most were defined as *strong*. ESO did not label expert opinions with strengths of recommendation, only indicating how many panel members agreed with the consensus statement. Most of the ESO consensus statements were agreed on unanimously. Overall, AHA/ASA had more

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Table 3. Main Topics of Agreement and Quality of Evidence Label

Topic	Recommendation	ESO Quality*	AHA Quality†
Extracranial vessel imaging	Use noninvasive vessel imaging to screen for stenosis of the cervical carotid	Very low	B-NR
Implantable monitoring	When the source after routine workup is undetermined	Low	B-R
Antiplatelet medication	Long term use is recommended, no preferred antiplatelet	Moderate	A
DAPT	Aspirin + clopidogrel for noncardioembolic minor ischemic stroke (NIHSS <4) or high-risk TIA ($ABCD^2$ >3)	High	A
Anticoagulants in nonvalvular atrial fibrillation	DOAC is preferred	High	A
Carotid endarterectomy	In severe (70–99%) symptomatic stenosis	High	A
	Preferred within 2 weeks	High	C-LD
Postacute interventions in dissection	An endovascular or surgical intervention may be considered when despite optimal medical management there are recurrent events	Consensus	C-LD
Intracranial atherosclerosis management	DAPT is reasonable for up to 90 days, recommend against anticoagulation. Recommend against endovascular therapy as first-line treatment	Very low	B-NR
	Recommend against initial angioplasty/stenting and surgery	Low	A
	Aggressive vascular risk factor control	Low	B-NR
LDL level	<70 mg/dL	High	A
Ezetimibe	Add ezetimibe in people do not achieve LDL-C targets despite taking maximally tolerated dose of a HMG-CoA reductase inhibitor	Consensus	A
Blood pressure target	<130/80 mmHg	High	B-R
HbA1c level	≤7%	Consensus	A
Pioglitazone	Pioglitazone may be considered	Moderate	B-R

AHA/ASA indicates American Heart Association/American Stroke Association; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulants; ESO, European Stroke Organization; HbA1c, hemoglobin A1c; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale/Score; and TIA, transient ischemic attack.

*The quality of evidence in ESO guidelines was rated from *high* through *moderate* and *low* to *very low*.

†The quality of evidence in AHA/ASA guidelines was graded from *A* (high quality), through *B-R* and *B-NR* (randomized or nonrandomized) to *C-LD* and *C-EO* (limited data or expert opinion).

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strong recommendations with low-quality evidence or expert opinion.

MAJOR TOPICS OF AGREEMENT AND DISAGREEMENT

Agreement

Regarding the major topics, 16 recommendations were comparable in both guidelines, although there were differences in the levels of evidence that the guidelines appointed, 11 (69%) were based on randomized studies (Table 3). First, both guidelines recommend noninvasive vessel imaging to screen for cervical carotid stenosis. Interestingly, the ESO indicated this to be low-level evidence, whereas the AHA/ASA denotes it as strong evidence (*Class 1*). Both guidelines suggest considering long-term monitoring if etiology of stroke or TIA remains unknown, and suggest use of an implantable loop recorder. This is especially interesting considering the absence of studies showing clinical benefit of this approach.[19] Moreover, both agree about long-term indications for antiplatelet therapy after stroke, and, in case of nonvalvular AF, prescription of a direct oral anticoagulant (DOAC). Neither guideline made a recommendation for a specific antiplatelet agent (aspirin, clopidogrel or aspirin combined with dipyridamole) or DOAC.

Both guidelines also agree on dual antiplatelet therapy ([DAPT] ie, aspirin and a P2Y12 [purinergic receptor P2Y G-protein coupled 12] inhibitor) in patients with minor stroke or TIA with high ABCD2 scores (>3). Nonetheless, there is discrepancy in the guidelines regarding the precise timing for initiating dual antiplatelet therapy. While the ESO recommends initiation within 24 hours after symptom onset, AHA/ASA suggests it should ideally commence within 12 to 24 hours. They added that dual antiplatelet therapy should be initiated within 7 days of onset at the very least, despite the absence of supporting evidence.

Based on expert opinion (ESO) and low-level evidence (AHA/ASA), both guidelines recommend considering nonacute endovascular or surgical interventions for cervical artery dissections in case of recurrent events despite medical management. Both guidelines made similar statements based on intracranial atherosclerotic stenosis, based on low levels of evidence or consensus. Moreover, both guidelines agree regarding specific blood pressure, low-density lipoprotein (LDL), and hemoglobin A1c targets for secondary prevention, as well as in adding ezetimibe when LDL targets are not reached.

Table 4. Main Topics of Disagreement

Topic	Recommendation		Evidence Quality	
	ESO	AHA/ASA	ESO*	AHA†
Timing of TIA review	Neurologic review <24 hours from event	Neurologic review <48 hours from event	Low	B-NR
Left atrial appendage occlusion	Insufficient data	Consider percutaneous closure of the left atrial appendage with the Watchman device to reduce bleeding risk of anticoagulation in patients who have contraindications for lifelong anticoagulation but can tolerate at least 45 days.	–	B-R
CEA in moderate stenosis (50–69%)	Suggest if symptomatic independent of age and sex.	CEA depending on patient-specific factors such as age, sex, life expectancy, and comorbidities.	Low	B-R
Carotid procedure risk threshold	The independently assessed risk of in-hospital stroke or death following endarterectomy or stenting for symptomatic carotid stenosis should be as low as possible, ideally below 4%.	Provided that perioperative morbidity and mortality risk is estimated to be <6%.	Consensus	A
PCSK9 inhibitors	There is continued uncertainty regarding the use of ezetimibe and/or PCSK9 inhibitors to reduce risk of recurrent stroke.	In very high-risk patients (defined as *stroke plus another major atherosclerotic cardiovascular disease or stroke plus multiple high-risk conditions*), are taking maximally tolerated statin and ezetimibe therapy and still have an LDL-C >70 mg/dL, it is reasonable to treat with PCSK9.	–	B-NR

AHA/ASA indicates American Heart Association/American Stroke Association; CEA, carotid endarterectomy; ESO, European Stroke Organization; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; and TIA, transient ischemic attack. – indicates that no recommendation was made because of insufficient data.

*The quality of evidence in ESO guidelines was rated from *high* through *moderate* and *low* to *very* low.

†The quality of evidence in AHA/ASA guidelines was graded from *A* (high quality), through *B-R* and *B-NR* (randomized or nonrandomized) to *C-LD* and *C-EO* (limited data or expert opinion).

Disagreement

There were only few issues of disagreement. For these recommendations, the level of evidence was mostly low or insufficient, although again disagreement was evident between both guidelines for their level of evidence label (Table 4). For TIA evaluation, ESO advises a specialist review in a TIA clinic within 24 hours. AHA/ASA states "a diagnostic evaluation is recommended for gaining insights into the etiology of and planning optimal strategies for preventing recurrent stroke, with testing completed or underway within 48 hours," but does not state how or by whom this should be performed. Regarding carotid endarterectomy in symptomatic moderate stenosis, AHA/ASA recommends taking into account multiple patient characteristics whereas ESO does not. ESO also states lower complication thresholds (based on expert consensus) for carotid interventions than AHA/ASA does (based on level A evidence). Guideline differences also were noted regarding the recommendations on recommendations for left atrial appendage occlusion and use of PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors. The difference

Table 5. Knowledge Gaps by Topic

Topic	Knowledge gap
Stroke and TIA workup	Optimal duration of prolonged rhythm monitoring Minimal duration of atrial fibrillation that increases stroke risk and would benefit from oral anticoagulation remains unknown. Multiple studies are ongoing. In whom to perform echocardiography, and in which patients transesophageal echocardiography is useful Exact definition of ESUS, optimal workup, and treatment strategy in these patients
Antiplatelet treatment	Best antiplatelet for secondary prevention and possible role for novel antiplatelet agents (ie, cilostazol and ticagrelor) The usefulness of CYP2C19 determination in patients with a new cardiovascular event already using clopidogrel Optimal strategy for TIA/ischemic stroke patients already on antiplatelet medication
Management of cardiac sources	Safety of DOAC in the setting of microhemorrhages and cerebral amyloid angiopathy remains unknown and merits further study Timing of anticoagulation start after ischemic stroke and optimal management before start of anticoagulation. Optimal management of ischemic event in patients with atrial fibrillation and a previous intracerebral hemorrhage Safety of discontinuing oral anticoagulation after surgical appendage closure is uncertain after the 45-day period Optimal treatment strategy in case of cardiac tumors
Extracranial carotid interventions	The natural history and the optimal medical vs surgical management of fibromuscular dysplasia and carotid webs
Dissection	Optimal management of carotid dissection with aneurysm formation
Intracranial artery disease	Preconditioning and permissive/induced hypertension in intracranial stenosis The natural disease course and optimal stroke risk factor mitigation strategies in Moya Moya disease
Other secondary prevention recommendations	Optimal treatment strategy in case of floating thrombus

DOAC indicates direct oral anticoagulants; ESUS, embolic stroke of unknown source; and TIA, transient ischemic attack.

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in stance of both guidelines on PCSK9 inhibitors might be explained by the fact that AHA/ASA determined "that many of these prevention strategies were important to include in any guideline related to the prevention of recurrent stroke. There is often no reason to think that the mechanisms of stroke prevention and benefits would be different in primary versus secondary prevention, although not studied within a purely secondary stroke prevention trial." For these recommendations, the level of evidence was downgraded. ESO decided not to use this evidence, since it was not specifically studied in stroke patients.

COMPARING GUIDELINES BY TOPIC

Stroke and TIA Workup

In the AHA/ASA guideline there is a dedicated section on diagnostic stroke workup.[15] There are no ESO guidelines/sections on diagnostic evaluation for secondary stroke prevention; therefore we used sections of the ESO's TIA and AF screening guidelines regarding the specific stroke workup elements.[10,13] There were no ESO statements regarding laboratory, standard brain imaging, transcranial doppler, ECG, and echocardiography. In the AHA/ASA guideline, troponin is suggested to be included in basic laboratory tests for stroke workup, but this is not stated in the recommendation table of the same guideline. No references or background information regarding troponin assessment were provided. Both guidelines gave no recommendations regarding standard cardiac monitoring, but did address prolonged cardiac monitoring. AHA/ASA recommends the evaluation of patients with TIA within 48 hours, whereas ESO recommends evaluation within 24 hours, based on low-level evidence. Additionally, ESO suggests against the use of the ABCD prediction tools. See Table S1 for further information.

Antiplatelet Treatment

Regarding antiplatelet treatment, we used elements of 2 ESO guidelines and the focused ESO guideline regarding DAPT.[7,8,10] Recommendations concerning intracranial atherosclerosis and dissections are discussed separately (see the Dissection and Intracranial Artery Disease sections). Both guidelines agree on the use of long-term antiplatelet management to reduce recurrent stroke. ESO made no statements regarding the specific antiplatelet medication, noting that their "recommendations cover use of antiplatelet therapy generally and choice of drug regimen may differ in some regions." AHA/ASA name 3 options: aspirin 50 to 325 mg, clopidogrel 75 mg, and aspirin 25 mg with extended-release dipyridamole 200 mg twice daily. Regarding timing, ESO states, based on low-level evidence, antiplatelet medication can be started prehospital in patients with TIA if a delay >24 hours to imaging is foreseen (no AHA/ASA statement).

Regarding DAPT, both guidelines recommend a short-term combination of clopidogrel and aspirin in certain stroke and TIA patients (based on high-level evidence), although there is disparity about the specific duration. A combination of ticagrelor and aspirin is also recommended by both guidelines (based on low-level evidence), although the exact subgroup of patients in whom this recommendation is applicable differs between guidelines. The ESO guidelines adheres to the THALES (Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and Aspirin for Prevention of Stroke and Death) trial criteria, where AHA/ASA chooses the 30% ipsilateral stenosis recommendation based on the THALES subgroup analysis.[20] ESO adds to this: "However, <10% of patients were included in the trial due to a TIA. This should be considered when deciding on a [DAPT] regimen after minor stroke and TIA. People with high-grade carotid stenosis and planned revascularization were excluded from POINT [Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke], CHANCE [Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events], and THALES." See Table S2 for further information.

Management of Cardiac Sources

The ESO guideline was published in 2019, whereas that from AHA/ASA was published in 2021.[11,15] Both guidelines agree that DOACs are now the preferred treatment strategy for nonvalvular AF. For antithrombotic treatment in patients with a history of intracerebral hemorrhage, ESO provides an expert opinion but AHA/ASA issues no statement. Regarding patent foramen ovale (PFO) closure and atrial thrombus, AHA/ASA issues expert opinion and low-level evidence statements, whereas ESO makes no recommendations. According to the ESO website "PFO management" is a guideline in development. Regarding left atrial appendage occlusion, ESO concludes that no recommendations could be made, but AHA/ASA states, that it may be considered in certain patients. Interestingly, both conclusions were based on the exact same studies. See Table S3 for further information.

Extracranial Carotid Interventions

The ESO guideline was published in 2022 and the AHA/ASA guideline 1 year earlier. The studies which formed the basis for the suggestions and recommendations were the same.[6,15] The ESO made no statements regarding vertebral artery disease. AHA/ASA guidelines conclude that optimal medical management is recommended, and that in case of symptoms despite optimal management, the usefulness of stenting or surgery is "not well established."

Statements were based on varying degrees of quality of evidence and expert opinions. Statements regarding

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carotid endarterectomy were underpinned by a high level of evidence, whereas statements pertaining to carotid artery stenting (CAS) had a low level of evidence. Both guidelines agree on the recommended stenosis grades for intervention in symptomatic stenosis and, if an intervention is indicated, to do so within 2 weeks. However, for the moderate stenosis grade, the AHA/ASA guideline adds that independent patient factors should be taken into account. For asymptomatic patients, ESO uses minimal stenosis grade of 60%, while the AHA/ASA has no recommendations on asymptomatic stenosis. Regarding CAS with asymptomatic stenosis, AHA/ASA also indicates 60% if observed with angiography. Regarding CAS, where the evidence level is lower, the AHA/ASA guidelines give more options to perform CAS, especially in terms of the statements in asymptomatic stenosis, where the ESO guidelines recommend against CAS and the AHA/ASA guidelines indicate that "it might be considered." ESO additionally recommends that CAS be performed only after careful consideration and multidisciplinary team meeting. See Table S4 for further information.

Dissection

Both guidelines were published in 2021 so the same data was available when making the guideline recommendations and suggestions.[9,15] There was only one randomized trial regarding dissection treatment.[22] Most statements were based on very low evidence, or expert opinion. Both guidelines agree that antithrombotic treatment is indicated in symptomatic dissections. However, based on the same evidence, the ESO guidelines leave the choice regarding the specific antithrombotic treatment choice to the treating physician, whereas the AHA/ASA guidelines specifically recommend aspirin or warfarin. Regarding duration of medication, ESO did not address this using a PICO-based query, stating: "There is no good information on the duration of antithrombotic treatment in [extracranial artery dissection] patients. No novel data has emerged to warrant an update on this matter. Of note, in the 2 [randomized controlled trials] on [eosinophilic-associated disease], the randomized intervention (anticoagulants or antiplatelets) had a duration of 3 months."

Both guidelines agree that an endovascular or surgical intervention may be considered in recurrent events despite medical management. Although the ESO based this recommendation on expert opinion, the AHA/ASA considered it Level 2b evidence. See Table S5 for further information.

Intracranial Artery Disease

The ESO guidelines were published in 2022, whereas the AHA/ASA guideline was published 1 year prior.[12,15] Nevertheless, the papers used in the suggestions and recommendations in the table are comparable. Based on moderate-level evidence, both guidelines suggest using antiplatelet medication instead of oral anticoagulants. Both guidelines suggest DAPT for 90 days, based on low-level evidence (no randomized trials). AHA/ASA states it is reasonable based on evidence labeled as *B-NR*, where ESO indicated that it was "weak for intervention" based on low-level evidence. The AHA/ASA guidelines use different DAPT strategies stratifying for various subgroups, whereas ESO did not use these further specifications, given the low level of evidence. Both guidelines recommended against angioplasty, stenting, or neurosurgery. Based on expert opinion, both sets of guidelines suggest that endovascular procedures should only be considered in recurrent events despite optimal medical management. Both guidelines had comparable statements regarding vascular risk factor management. ESO also made a statement on preconditioning and permissive hypertension based on a low level of evidence and expert opinion. See Table S6 for further information.

Other Secondary Prevention Recommendations

The ESO guideline was published in 2022, and the AHA/ASA guideline 1 year earlier. Both guideline recommendations were based on the same evidence. The use of lifestyle measures to prevent stroke will be discussed in future ESO guidelines, which were not yet available at the time of writing this article. ESO has a joint guideline statement regarding sleep. No strength or level of evidence is appointed to the statements in that paper.[5,15] Most statements regarding medical management were based on high- to moderate-level evidence, and some on expert opinions.

Both guidelines agree on the level of LDL, blood pressure and glucose targets. Of note is the major contrast in recommendations concerning ezetimibe and PCSK9 inhibitors. ESO concludes that there is no specific evidence to warrant their use in ischemic stroke, thus only formulating expert opinions. AHA/ASA's level-of-evidence ranges from *strong* to *moderate*. Regarding blood pressure, ESO makes no statements regarding type of blood pressure medication, where AHA/ASA has strong recommendations for specific antihypertensive drugs. Both guidelines agree there is a possible benefit of pioglitazone. See Table S7 for further information.

Knowledge Gaps and Areas of Uncertainty

There are issues on which neither guideline provides recommendations, or that are otherwise pointed out as remaining knowledge gaps by the guidelines (Table 5). A recent trial, ELAN (Early Versus Later Anticoagulation for Stroke With Atrial Fibrillation), on the timing of anticoagulation after ischemic stroke was published after

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both sets of guidelines. This study provides more data on this subject, although the definite optimal timing to initiate anticoagulation medication in cases of newly diagnosed AF remains uncertain.[21,22] It is also debatable whether the strong level of evidence for carotid endarterectomy in symptomatic significant stenosis is still up to date, considering the advancements made in secondary prevention measures for ischemic stroke. Ideally, more data is needed with direct comparison of surgical interventions with current medical therapy. Additionally, multiple knowledge gaps remain for PFOs, as outlined in the AHA/ASA guidelines. For example, it is not known whether PFO closure is better than long-term anticoagulation, what to do in patients ≥60 years of age, and what to do in cases of a remaining shunt after PFO closure. ESO recently published a guideline on Moya Moya disease, but most recommendations were consensus statements because of the low level or lack of evidence.[23]

DISCUSSION

This article shows that most ESO and AHA/ASA guideline recommendations for stroke workup and secondary prevention were similar; however, not all were based on high-level evidence and the appointed level of evidence often differed. Unfortunately, no specific recommendations could be made on many topics, which is a result of absent or insufficient evidence; some topics were not mentioned in either guideline.

How should clinicians interpret these guidelines and apply them to their daily clinical practice? Both stroke organizations clearly defined and stated how the recommendation were labelled and how the guideline recommendations were put together. All recommendations are accompanied by a level-of-evidence label. When comparing all statements of both guidelines on stroke workup and prevention, ESO exhibited a more cautious stance in determining the threshold for what constituted sufficient evidence, resulting in many more expert opinions or in some cases even no statement due to insufficient evidence. For recommendations with low level of evidence, AHA/ASA frequently used words to modulate the strength of the recommendations (eg, *consider*, *reasonable*, and *suggest*). In general, we found that AHA/ASA had a tendency to appoint higher levels of evidence for the recommendations than did ESO. Of the 10 *Level A* evidence (high quality) recommendations in the AHA/ASA guidelines, the ESO only labeled 4 as *high* (Table 2). There was 1 statement that ESO labeled *high*, of which the AHA/ASA labeled *C-LD*.

The setup of the guidelines is quite different. The AHA/ASA guideline is 1 large document covering everything stroke clinicians need to know about stroke care, while the ESO guidelines are mostly summarizing and comparing evidence in order to answer specific PICO questions. This may also explain why the AHA/ASA has considerably more recommendations than the ESO, and that, in areas of uncertainty, the AHA/ASA tries to provide the clinician with helpful practical advice, whereas ESO often refrains from forming definitive statements, considering the same underlying evidence as insufficient. In this way, AHA guidelines are more directly aimed on the needs of the consumer (ie, the practicing stroke physician).

Taking into account the degree of guideline concordance and the level of evidence behind the recommendations may help clinicians, researchers and policy-makers to prioritize specific treatments and interventions to improve guideline adherence. Interestingly, there were many differences between the level of evidence appointed by the guidelines to the same recommendations. Most notably this difference was found in the topics where guidelines had different recommendations. The observed divergence in recommendations are not explained by different release dates of guidelines (ie, they were not evaluating different studies). Consequently, differences are more likely to be explained by different frameworks for interpreting evidence and putting medical research into clinical practice. In case where guidelines diverge, it is no surprise that considerable practice variation exists between countries, hospitals, and providers. A more reliable framework for adjudicating strength of evidence may help clinicians implement guidelines. For the clinician it is important to know what recommendations are based on solid evidence and where they are not, to make informed decisions with and for their patients.

Similar recommendations that are based on strong evidence in both guidelines should be implemented in clinical practice. Similarly, we also recommend implementing recommendations found in even just one of the guidelines (AHA/ASA or ESO) if they are supported by high-level evidence. If practice patterns deviate from concordant guidelines based on strong evidence, interventions to enhance implementation should be considered. Scenarios in which both guidelines agree—based on low-level evidence—present challenges for clinicians and policymakers. In these scenarios, the decision to adhere to these recommendations should be made by the treating clinician or stroke team, with careful consideration of patient preferences. In these instances, it may be reasonable to diverge from the guidelines, particularly if patient factors or preferences make a specific treatment more or less valuable. Some of these recommendations include: prolonged DAPT for intracranial atherosclerosis, ezetimibe, and use of implantable rhythm monitoring. Similar logic applies for recommendations where guidelines are discordant, most often resulting from lack of robust evidence. These are often statements containing the terms *consider*, *reasonable*, and *suggest*, or expert opinions. For decisions on topics with no robust evidence, the treating clinician should not blindly follow these recommendations. When these

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are often-encountered clinical issues, local or regional stroke teams could decide on what to do in these areas of uncertainty. However, deviating from guidelines with low-level evidence is only recommended when done consistently based on a publicly available, well-wrought protocol that is locally, regionally, or nationally registered, otherwise unwanted and unnecessary practice variation will result.

Finally, there are remaining issues with no or insufficient evidence, and topics that are not covered by either guidelines. As discussed in this article, these issues include best antiplatelet medication, usefulness of CYP2C19 (cytochrome P450 2C19) determination, timing of anticoagulation after stroke, who needs echocardiography, duration of prolonged rhythm monitoring and optimal treatment of floating thrombus, carotid web, fibromuscular dysplasia, Moya Moya, and carotid dissection. Ideally, further research will help to determine how to handle these subjects and to harmonize clinical practice. However, areas of uncertainty do not only contain recent subjects that could be further studied in the near future, but also subjects regarding specific decisions in ischemic stroke scenarios that are uncommon, and so these will remain difficult to evaluate in clinical studies. Also, here the stroke physician should make the best possible (individualized) treatment choice. Possible solutions are to make or share simple local protocols, and a whenever possible use multidisciplinary team meetings for decision making especially concerning interventions.

Suggestions for Improvement

Harmonization of the US and European guidelines—and possibly other international guidelines in the future—would be helpful. Guideline harmonization results in a more unified message to clinicians, patients, researchers, and policy makers. This will lead to less practice variation and more focused research into areas of current uncertainty.[4] Hopefully, such an improved international work force may result in joint research efforts. For example, in case of low frequency clinical scenarios, where randomized trials are unlikely to be performed, this may also lead to prospective international registries to help address these issues.

Second, the current format of the ESO and AHA/ASA guidelines lack the possibility to continuously incorporate novel research findings with clinical implications. Findings from new trials that are published after publication of the most recent guidelines will only be incorporated when a guideline is updated, a process typically taking several years after the last publication. Therefore, adhering to guidelines could possible lead to outdated treatments and procedures to be carried out on our stroke patients. "Living guideline" approaches could resolve this issue, through continual surveillance of the evidence and rapid incorporation of new evidence, using living systematic review methods.[24] The Australian and New Zealand joint guideline already uses a Living Guideline platform, enabling rapid updates to subsections without having to update the entire document continuously (https://informme.org.au/guidelines/living-clinical-guidelines-for-stroke-management).

Limitations

Our review has limitations. First, it is possible that we have failed to identity some specific guideline recommendations, although these risks are mitigated given the standardized dissemination platforms for both relevant guidelines and generally similar underlying language ad concepts. Second, determining guideline concordance requires a degree of subjective judgement and it is possible that others may diverge with our judgements. We sought to minimize this by having multiple authors participate in this process. Third, the scope of our review is explicitly narrow and may not generalize to guideline differences at different times or in different clinical contexts. Lastly, we only considered guidelines from Europe and the United States: guidelines from other parts of the world were not considered. Additionally, there are national guidelines, and even regional and hospital guidelines (eg, in the Netherlands). This implies that there is even more variability than noticed in our paper.

CONCLUSIONS

In conclusion, most ESO and AHA/ASA guideline recommendations for stroke workup and secondary prevention were similar. However not all were based on high level of evidence and the appointed level of evidence often differed. One noticeable difference was that AHA/ASA also used indirect evidence from cardiovascular studies, were ESO only used evidence from studies in the stroke populations. Unfortunately, for many topics, no specific recommendations could be made resulting from the absence or insufficiency of evidence; some topics were not mentioned in either guideline. Clinicians should not blindly follow all guideline recommendations, the accompanying level of evidence inform which recommendations are based on robust evidence. Topics with lower levels of evidence, and where recommendations disagree or are missing may incentivize further clinical research.

ARTICLE INFORMATION

Received March 16, 2024; accepted May 29, 2024.

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Sources of Funding

None.

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Disclosures

Dr Dippel reports grants from Stryker, Medtronic, Penumbra, Cerenovus, and Thrombolytic Science, paid to the institution for research outside the submitted work.

Supplementary Material

Tables S1–S7

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